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Original Investigation

Kidney Stones and Cardiovascular Risk: A Meta-analysis of Cohort Studies

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Background: Recent epidemiologic evidence suggests an association between kidney stones and incident cardiovascular disease after adjusting for other cardiovascular risk factors, but results are inconsistent.

Study Design: Meta-analysis of cohort studies.

Setting & Population: Patients with kidney stones.

Selection Criteria for Studies: Cohort studies with data for kidney stones and cardiovascular morbidity identified in PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and conference proceedings through February 27, 2014.

Predictor: Kidney stones as determined by physician diagnosis, clinical coding, or self-reported scales.

Outcomes: Cardiovascular disease, coronary heart disease (CHD), and stroke.

Results: 6 cohort studies that contained 49,597 patients with kidney stones and 3,558,053 controls, with 133,589 cardiovascular events, were included. Pooled results suggested that kidney stones were associated with an increased adjusted risk estimate for CHD (HR, 1.19; 95% CI, 1.05-1.35; $P = 0.05$; n = 6 cohorts) and stroke (HR, 1.40; 95% CI, 1.20-1.64; $P < 0.001$; n = 3 cohorts). In particular, kidney stones conferred HRs of 1.29 (95% CI, 1.10-1.52; n = 6 cohorts) and 1.31 (95% CI, 1.05-1.65; n = 4 cohorts) for myocardial infarction and coronary revascularization, respectively. Moreover, the pooled female cohorts showed a statistically significant association (HR, 1.49; 95% CI, 1.21-1.82; n = 4 cohorts), whereas the male cohorts showed no association (HR, 1.15; 95% CI, 0.89-1.50; n = 2 cohorts).

Limitations: Results may be limited by substantial heterogeneity, likelihood of residual confounding, and paucity of studies that separately evaluated for effect modification by sex.

Conclusions: Kidney stones were associated with increased cardiovascular risk, including the risk for incident CHD or stroke. There is some suggestion that the risk may be higher in women than men. Further prospective studies are needed to determine whether the association is sex specific.

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INDEX WORDS: Cardiovascular; coronary heart disease (CHD); kidney stones; meta-analysis; stroke; risk factor; nephrolithiasis; renal calculus.

Kidney stone disease is a common painful condition occurring in the general population. It affects approximately 1 in 11 people in the United States,[1] and the prevalence has increased from 3.8% (1976-1980)[2] to 8.8% (2007-2010).[1] Kidney stones increasingly have become recognized as a systemic disorder[3] associated with diabetes mellitus, obesity, hypertension, hyperuricemia, hypercholesterolemia, and chronic kidney disease.[2,4-6] All the aforementioned conditions are known risk factors for cardiovascular disease, and epidemiologic studies also have suggested that kidney stones and coronary heart disease (CHD) may share common underlying risk factors.[4]

It has been hypothesized that kidney stones are associated with increased cardiovascular risk, especially the risk for CHD and stroke. In a cohort study with a mean follow-up of 9 years, a 31% increased risk for myocardial infarction (MI) was observed in patients with kidney stones after adjusting for chronic kidney disease and other comorbid conditions.[7] Another cohort study reported that patients with kidney stone had a 33% increased risk for MI and stroke compared with the general population.[8] It also has been suggested that pathophysiologic pathways that lead to calcium kidney stones also may contribute to coronary artery calcification, which is a risk factor for cardiovascular events.[9,10] Despite the potential physiologic mechanisms, epidemiologic studies have produced mixed results for the association of kidney stones with cardiovascular risk, with some having reported a positive relationship[7,8,11-13] and other failing to demonstrate a significant association.[14] Even in the

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same study, differential associations were found according to sex-specific cohorts.[15]

Given the common incidence of kidney stones and the serious outcomes of cardiovascular events, we aimed to summarize the association between kidney stones and cardiovascular risk in cohort studies by performing a detailed meta-analysis. Better understanding of the relationship also may highlight the importance of considering additional intervention methods in this area.

METHODS

This study was performed according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology)[16] reporting guidelines.

Data Sources and Searches

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases (last update on February 27, 2014) to identify eligible studies using the Medical Subject Headings (MeSH) search terms and key words "renal stones" or "renal calculus" or "kidney stones" or "kidney calculi" or "nephrolith" or "nephrolithiasis" and "coronary heart disease" or "cardiovascular disease" or "cardiovascular events" or "coronary occlusion" or "myocardial ischemia" or " myocardial infarction" or "ischemic heart disease" or "angina pectoris" or "stroke" or "CVD" or "CHD" or "MI" and "risk" or "incidence" or "epidemiology." Item S1 (provided as online supplementary material) shows details of the search method. No language restrictions were imposed. We also reviewed abstracts submitted to the American Society of Nephrology's annual Kidney Week meetings (2003-2013) and the American Urological Association annual meetings (2009-2013), as well as bibliographies of retrieved articles and using the PubMed related articles option.

Eligibility Criteria and Study Selection

Studies were included if they met all the following inclusion criteria: (1) cohort design; (2) assessed the incidence of cardiovascular disease, CHD (defined as fatal or nonfatal MI or coronary revascularization), or stroke among patients with kidney stones; and (3) provided the multivariate-adjusted (at least adjusted for 5 of 7 factors: age, sex, body mass index, hypertension, diabetes, lipid levels, and smoking) hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs) for events associated with kidney stones versus controls. Case-control or cross-sectional studies, literature reviews, comments, editorials, and case reports were excluded. Three authors (Y.L., S.L., and Z.Z.) independently evaluated all records by title and abstract and subsequently retrieved and assessed in detail the full text of any potentially relevant articles using the mentioned criteria for eligibility. No restrictions were imposed on language, sample size, or study duration. When multiple reports of the same population or subpopulation were identified, only the most recent report was included. Disagreements regarding eligibility were resolved through discussion with 2 additional adjudicators (J.W. and L.X.) and by referencing the original report.

Data Extraction and Quality Assessment

Data were extracted from eligible articles onto a standardized form independently by 2 reviewers (T.L. and Y.H.). Disagreements were resolved through consensus and arbitration by a third author (S.L.). The following data were extracted: first author's name, year of publication, country of origin, population source, mean age, study duration, median follow-up period, sample size, number of outcomes for those with and without kidney stones, events for analysis, adjustment factors, and multivariable-adjusted risk estimates and their 95% CIs. The methodological quality of cohort studies was assessed by 2 authors independently (X.Q. and Y.L.) using the Newcastle-Ottawa scale.[17] This scale assesses the quality of observational studies and allocates a maximum of 9 points for quality of selection (up to 4 points), comparability (up to 2 points), and outcome (up to 3 points) of study participants. Overall study quality was arbitrarily defined as poor (score, 0-3), fair (score, 4-6), or good (score, 7-9). Disagreement was resolved by consensus.

Data Synthesis and Statistical Analysis

Data analysis used multivariate-adjusted outcome data (expressed as HRs and 95% CIs). We converted these values in every study by using their natural logarithms, and standard errors were calculated from these logarithmic numbers and their corresponding 95% CIs. For the statistical analysis, we combined log HRs and standard errors using the inverse variance approach. Pooled HRs with 95% CIs were estimated using a random-effects model of the DerSimonian and Laird method,[18] which assumes genuine diversity and adds an empirical estimate of the between-study variance (τ^2) to the between-study variance. Heterogeneity was tested by Cochran Q test and quantified by I^2 statistics (25%, 50%, and 75%, representing low, moderate, and high heterogeneity, respectively).[19,20] Sensitivity analyses were conducted to assess the robustness of results by sequential omission of individual studies.[21]

Our main analyses were risks of CHD and stroke incidence associated with kidney stones, respectively. CHD was defined as fatal or nonfatal MI and coronary revascularization. If the result for CHD was not provided, we used data from MI as a surrogate. A 2-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using STATA, version 12.0 (StataCorp LP).

RESULTS

Study Selection, Characteristics, and Quality

A summary of the study identification process is shown in Fig 1. Item S2 shows the list of studies excluded based on review of the full text. Six articles[7,11-15] were deemed eligible for this meta-analysis. Five articles were published in full[7,12-15] and one was in abstract form.[11] Study characteristics of included cohorts are listed in Table 1, and study outcomes and effect estimates for the association of kidney stones and cardiovascular risk from each included study are listed in Table 2. Included articles were published in 2005-2014. These 6 studies included 49,597 patients with kidney stone disease and 3,558,053 controls. Six cohorts reported results for CHD (MI or coronary revascularization),[7,11,13,15] and 4 cohorts, for stroke.[12-14] Median duration of follow-up was 8.9 (range, 5-13.7) years. All studies adjusted adequately for potential confounders (at least 5 of 7 factors: age, sex, body mass index, hypertension, diabetes, lipid [or fat] levels, and smoking). According to the Newcastle-Ottawa scale, all cohort studies were considered of fair (scale, 4-6) to good (scale, 7-9) quality (Table 3).

Risk of Kidney Stones on CHD Events

The multivariate-adjusted relative risks for incident CHD with kidney stones versus controls for each